REMARKS

Of claims 1-68 which were contained in the original application, claims 37-50, drawn to lysosomal acid lipase and pharmaceutical compositions thereof, claims 51-63, drawn to gene therapy with the gene for lysosomal acid lipase, claim 64, drawn to a method of treating Wolman's disease with lysosomal acid lipase, and claim 65, drawn to a method of treating cholesteryl ester storage disease with lysosomal acid lipase, have been withdrawn from further consideration, as being drawn to non-elected inventions. Applicants reaffirm the election of Group I and Group II claims, with traverse. Of the Group I claims (claims 1-18), claims 5-9 have been cancelled herein and claims 1-4, and 10-18, which are drawn to reducing atherosclerotic plaques in a mammal, remain under consideration. Of the Group II claims (claims 19-36 and 66-68) , claims 23-27 have been cancelled herein and claims 19-22, 28-36 and 66-68, which are drawn to a method of treating atherosclerosis in a mammal with exogenously produced lysosomal acid lipase, remain under consideration.

Claims 1-2, 16-20, and 34-36 have been amended so as to define lysosomal acid lipase (LAL) as the lipid hydrolyzing polypeptide used in the claimed methods.

Before considering the rejections in detail, the fundamental concepts of the present invention will be briefly reviewed. The present invention comprises a method to diminish and/or eliminate atherosclerotic plaques in mammals, through direct and indirect treatment of these plaques, *in situ*, using proteins and/or polypeptides. Generally, compositions used for practicing this invention include lipid hydrolyzing proteins or polypeptides, and in particular, the protein lysosomal acid lipase (LAL). These proteins and/or polypeptides are capable of lipid removal, primarily through hydrolysis, either by a catalytic or stoichiometric process, wherein the lipid

hydrolyzing protein or polypeptide targets receptors in and/or on the cell leading to uptake into the lysosome. Exogenously produced lipid hydrolyzing proteins, contained in a pharmaceutically acceptable carrier, may be administered either orally, parenterally, by injection, intravenous infusion, inhalation, controlled dosage release or by intraperitoneal administration in order to diminish and/or eliminate atherosclerotic plaques. The preferred method of administration is by intravenous infusion.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1-2, 3-8, 16-22, 24-26 and 34-36 under 35 U.S.C. §112, first paragraph, maintaining that while the specification is enabling for LAL, it does not reasonably provide enablement for any lipid hydrolyzing polypeptide and accordingly, does not enable any person skilled in the art to which it pertains to make and or use the invention commensurate with the scope of the claims. While Applicants do not agree with the Examiner's position, in order to more clearly define the instant invention, claims 1-2, 3-8, 16-22, 24-26 and 34-36 have been amended to define the processes using lysosomal acid lipase as the lipid hydrolyzing polypeptide. Thus, since the Examiner states that the specification *is enabling* for LAL, this rejection under 35 U.S.C. 112, first paragraph, is now moot and should be withdrawn.

Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 1-36 and 66-68 under 35 U.S.C 103(a) as being unpatentable over Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993), Walters et al. (1994) and Escary et al. (1998) in view of Coates et al. (1986).

In making this rejection, the Examiner maintains that since Coates et al. established that deficiencies in LAL increased the risk of developing atherosclerosis, thereby suggesting that remedying such a deficiency could constitute an effective therapy for atherosclerosis, and, given the combined teachings of Chan et al., Bond et al., Pomerantz et al., Walters (sic) et al., and Escary et al. (1998) which all provide examples where increasing LAL activity, albeit by secondary agents, reduces atherosclerosis, and, with the limited to non-existent success of gene therapy methods to date, it would have been obvious to a person of ordinary skill in the art to increase LAL levels by direct addition of the enzyme. Applicants respectfully traverse this rejection.

Chan et al. discuss the use of prostaglandins as potential therapeutic substances for various cardiovascular diseases including atherosclerosis. Chan et al. state that atherosclerosis may result from decreases in prostacyclin formation in the blood vessel wall due to inhibition by high concentrations of lipid peroxides in the blood and that prostacyclin stimulates cholesterol ester hydrolase. Accordingly, Chan et al. maintains that prostacyclin and other related prostaglandins may be useful for the prevention of atherosclerosis. In contrast to the present invention, prostaglandins are not polypeptides but rather are small, low molecular weight molecules. The proposed role of prostaglandins in the regulation/prevention of atherosclerosis is that they are thought to stimulate production of CEH (cholesterol ester hydrolase) for mobilization of cholesterol. Thus, the prostaglandins do not *directly* prevent atherosclerosis but rather play a *secondary role* in the mechanism for regulation/prevention of atherosclerosis in that they stimulate production of the polypeptide cholesterol ester hydrolase which is thought to play a key role in clearance of cholesterol.

Bond et al., Pomerantz et al., and Walters et al. (*sic*) each describe the use of calcium channel blockers (antagonists) for stimulation of cholesteryl ester hydrolase activity wherein cholesteryl ester hydrolase is thought to increase clearance of accumulated cholesterol. Again, as in the reference of Chang et al., these calcium channel blockers play only a secondary role in reduction of atherosclerotic lesions in that they stimulate production of the polypeptide cholesteryl ester hydrolase, which in turn is thought to play a role in clearance of cholesterol. This is in contrast to the present invention wherein clearance of cholesterol involves direct administration of the polypeptide lysosomal acid lipase.

Escary et al. teach that HSL (hormone-sensitive lipase) overexpression in macrophages alone or in combination with ACAT (acyl coenzyme A:cholesterol acyl transferase) inhibitors may constitute a useful therapeutic approach for impeding cholesteryl ester accumulation in foam cells in atherosclerotic lesions. This is in contrast to the present invention which involves the direct administration of lysosomal acid lipase for reduction of atherosclerotic lesions. In addition, Escary discusses the use of a *hormone*-sensitive lipase while the present invention relies on a *lysosomal* acid lipase for inhibition of atherosclerotic lesions. These two lipases function by different biochemical mechanisms within the cell. Hormone-sensitive lipase is found within the cytoplasm of the cell while lysosomal acid lipase is found within the lysosome.

Coates et al. teach that low acid lipase activity may represent an independent risk factor for the development of premature atherosclerosis due to inherited deficiencies in this enzyme. Coates et al. does not teach that direct administration of LAL would alleviate such a deficiency, nor does Coates suggest or motivate one skilled in the art to administer LAL in order to treat such a deficiency. Coates merely

suggests that there may be a *familial link* for low acid lipase activity due to an inherited allele which confers low enzyme activity.

In addition, it must be pointed out that the Examiner erroneously relies on comparisons of HSL with LAL. The references by Chan et al., Pomerantz et al., Walters et al., and Escary et al. (1998) are of a totally different enzyme. Accordingly, although the EC numbers of the two enzyme are the same, LAL and the neutral (or hormone sensitive lipase) have completely different sequences (gene and protein) and are compartmentalized differently. Thus the enzymes are different.

Finally, a subsequent publication by Escary (Escary et al., "Paradoxical Effect on Atherosclerosis of Hormone-Sensitive Lipase Overexpression in Macrophages," Journal of Lipid Research, vol. 40, pp. 397-404, 1999, see Supplemental IDS), discloses the surprising finding that macrophage-specific HSL (hormone-sensitive lipase) overexpression leads to **greater** susceptibility to developing atherosclerosis. This is exactly the opposite effect observed in the present invention – which is that exogenous administration of lysosomal acid lipase produces a **decrease** in atherosclerotic lesions. Accordingly, Escary et al. (1999) teaches away from the present invention in that it does not suggest or motivate one skilled in the art to administer an exogenous lipase in order to treat atherosclerotic lesions.

Thus, in view of the above arguments, the combined references of Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993), Walters et al. (1994) and Escary et al. (1998) in view of Coates et al. (1986), do not teach, suggest or motivate one skilled in the art to *directly* administer exogenous LAL in order to treat atherosclerotic lesions. The combined teachings of Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993), and Walters et al. are all directed to the use of secondary agents to stimulate production of cholesteryl ester hydrolase and do not teach or suggest direct

administration of the LAL polypeptide. In fact, the later teachings of Escary et al. (1999) teach away from the direct administration of LAL for the treatment of atherosclerotic lesions. In addition, Coates et al. simply provides evidence for an inherited autosomal mutation associated with reduced LAL activity and thus an independent risk factor for developemnt of atherosclerosis. Accordingly, none of these references, taken together, teach or suggest the present invention and the Examiner's rejection based on 35 U.S.C. §103 has been overcome and should be withdrawn.

In summary, the rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §103 have been overcome and should be withdrawn. Applicants have amended their claims to more clearly define the instant invention and not to avoid the Examiner's rejections. Accordingly, the present application as amended herein, is now in form for allowance and early reconsideration and allowance of the claims, as currently pending, is earnestly solicited.

Respectfully submitted,

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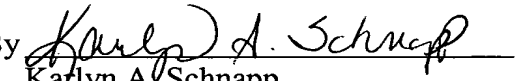
By 
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